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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,585	09/19/2001	Ali I. Fattom	018861-0216	8124

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,585	FATTOM ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 14-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The response and corrected amendment filed 8-6-04 and 10-22-04 respectively, have been entered into the record. Claims 2-13 have been cancelled. Claims 1 and 14-19 are pending. Claims 1 and 14-19 are under examination.

The text of Title 35 of the US Code can be found in the previous office action of record.

Rejections/Objections Withdrawn

The objections to claims 2, 3, 11 and 12 under 37 CFR 1.75(c) as being of improper dependent form is withdrawn in view of the amendments to the claims.

The rejection of claims 2 and 3 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the cancellation of the claims.

The rejection of claim 2 under 35 USC 102(b) as being clearly anticipated by Welsch et al (Journal of the American Society of Nephrology 7:247-253, 1996: reference A2 on PTOL-1449) is withdrawn in view of the cancellation of the claim.

Rejections/Objections Maintained

The objection to claim 1 and 14-19 as object to under 37 CFR 1.75 (c) as being in improper form because they include non-elected subject matter is maintained. It is noted that claim 1 is still directed in the alternate, to a glycopeptide bacterial surface antigen and immunocarrier.

Claims 1 and 14-19 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of protecting an immune-compromised end stage renal disease human patient from an infection by *Staphylococcus aureus* comprising administering a vaccine comprising a glycoconjugate of a polysaccharide and an

immunocarrier to the patient wherein the vaccine comprises glycoconjugates of both Type 5 and Type 8 polysaccharide antigens of *Staphylococcus aureus* and optionally an adjuvant, it does not reasonably provide enablement for protection of cancer patients, AIDS patients, diabetic patients, elderly, patients on immunosuppressive therapy, transplant patients, patients with surgical procedures, burn patients and other patients in acute care settings for reasons made of record in the Office Action mailed 4-7-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that immune-compromised patients with end stage renal disease (ESRD) is representative of the genus of immunocompromised patients. Applicants indicate that pages 11-12 teach that these types of immunocompromised patients will benefit from the administration of the vaccine according to the present invention. This is not persuasive, as previously pointed out, the specification lack any data regarding antibody production in these individuals of a type that correlates with protective activity (i.e. oposonization by PMN's). Applicants argue that the examiner overlooks the data in regard to the prototypical immune-compromised population of ESRD patients. Applicants argue that ESRD patients are reflective of the general population of immune-compromised patient population because many ESRD patients are unable to fix complement, many have phagocytes with weakened chemotactic response, suffer from uremia with impacts the functionality of granulocytes and complement fixation. Diabetics and uremia also impact the functionality of B cells. Applicants argue that ESRD patients represent the "worst-case scenario". This is not persuasive. ESRD patients, unlike immunosuppressed individuals, neonates, and the elderly and patients with immunodeficiencies have a competent T-cell and B-cell immune system. Immunosuppressed individuals (i.e. cancer patients), neonates and the elderly fail to respond because the specific arm of the immune system is unable to produce an antigen-specific response. Immunosuppressed cancer patients and transplant patients lack the ability to mount a T-and B-cell response to antigen because the immunosuppressive chemotherapy attacks all actively dividing cells.

Cell division and expansion is required by the specific-arm of the immune response in order to produce antibody. Hence, unlike ESRD patients, these cancer patients that are immunosuppressed are compromised, not because of the inability of the antibody to opsonise or cells to phagocytose, but because chemotherapy attacks dividing cells of all types. Immunosuppression results in decreased amount of all hematopoietic cells, because they are renewed on a daily basis. As such, ESRD patients are not directly comparable to cancer patients on immunosuppressive therapy as claimed. Applicants have not presented any evidence that the elderly in extended care facilities, diabetic patients, patients with invasive surgical procedures and other patients in acute care setting are 1) immune-compromised and 2) have the same deficiencies as the ESRD patients. Further, with respect to Diabetic patients, applicants' assertions with regard to an impact on B-cell function lack evidentiary support. Applicants argue that the some of the ESRD patients had diabetes, had graft access, were elderly as supported at page 16 paragraph [0053] in the specification. This is not persuasive, the specification does not provide any break down of the data with respect to the individual conditions claimed and therefore one skilled art is unable to ascertain the antibody levels of any subgenus of ESRD patients having diabetes, elderly, shunts etc. The specification does not provide the data with respect to any subgenera of ESRD patients. Further, the claims do not limit to patients with ESRD that have diabetes, shunts or are "elderly". Applicants argue that the relied upon statement that active immunization is unlikely to work in low birth weight neonates, or cancer, AIDS and burn patients who are strongly immunocompromised" is taken out of context and the next sentence teaches that hyperimmune immunoglobulin would be the treatment of choice in these patients and they are no beyond immunological means of protection. This is not persuasive, the claims are specifically drawn to active immunization by administration of the bivalent conjugate vaccine. The claims are not drawn to passive immunization and passive immunization is irrelevant to the claimed invention. Applicants have not shown protection in the cited populations, relied upon by the examiner.

Applicants argue that they have cancelled the specific recitation of neonates, AIDS patients and burn patients. This is not persuasive, claim 16 is still drawn to a neonate. Applicants argue that Chisholm et al (Arch. Dis. Child 84:496-500, 2001) teaches the successful vaccinations of cancer patients. This is not persuasive, the vaccine is not a capsular polysaccharide conjugate vaccine and the article teach is that "One remaining area of uncertainty is whether an antibody level of 40, normally considered protective in healthy individuals, is actually protective in the immunocompromised host." Chisholm et al teach that the reports on protection are conflicting (page 499, column 1, second full paragraph). As such, this article, while recommending immunization of children with cancer, falls short of indicating that the antibody level is actually protective in immune compromised hosts. The article is clearly uncertain on this point and indicates that there are contradictory reports in the art regarding vaccination of immunocompromised cancer patients. The bivalent vaccine has not been shown to be protective against other *Staphylococcal* species or *Enterococcal* species as is specifically claimed. The response in ESRD patients is specific to *S. aureus* and applicants' response is directed to protection against *S. aureus* and does not provide evidence with regard to the scope of the preamble and protection outside of *S. aureus*. Applicants' amendment does not obviate this issue.

In view of the foregoing, the rejection is maintained.

Claims 1, 14, 15 and 17 stand rejected under 35 USC 102(b) as being clearly anticipated by Fattom et al, (Annals of Medicine, 28:43-46, 1996: reference A3 on PTOL-1449) is maintained for reasons made of record in the Office Action Mailed 4-7-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the claims require that the composition be protective and that the relationship between immunogenicity and protection is always uncertain. This is not persuasive, the relationship between induction of antibodies and protection from infection has been well established in humans using the claimed vaccine. Applicants are directed to

all the art of record and the teaching of the specification that indicates that antibodies to Types 8 and 6 and 336 CPS induce type-specific opsonophagocytic killing by human PMNs *in vitro* and confer protection in animal infection models (page 2, [0005]). As such, the association between antibody production and protection from infection was established in relevant models. Further, such arguments are not persuasive because the identical composition was administered to the claimed population of patients. Since there is no difference between composition administered and the patient population, the function of vaccine is an inherent property. Thus, the art practiced the invention more than one year before the instant filing date. Applicants argue two additional papers that evidence the significant difference between the production of antibodies and protection from disease. These are not persuasive to remove the rejection of record because they are drawn to a vaccine that is different than the instantly claimed vaccine preparation. With respect to Romero-Steiner et al, it is noted that a glycoconjugate vaccine was not used in the studies. It is noted that the glycoconjugate vaccines are structurally different from the naked polysaccharide vaccines that have largely been abandoned in favor of glycoconjugate vaccines that produce a better quality antibody. As such, the studies presented therein are not directly comparable to immunization with a glycoconjugate vaccine. With respect to Musher et al, it is noted that in contrast to Applicants' assertions, it was found that most patients with disease lacked detectable IgG at admission to the infecting serotype of the bacterium. Therefore, one cannot make a conclusion that the production of antibodies was not protective, because the individuals had no antibody present in the serum and it is well known that, as with *Staphylococcus aureus*, that serotypes from *Streptococcus* are not crossprotective. Applicants argue that Musher et al teaches that patients IgG had diminished capacity to opsonise bacteria. This is also not persuasive, Applicants are comparing apples and oranges. Musher et al compares vaccination-induced IgG with convalescent IgG. Further, Musher et al links oposinization with protection from disease. It is noted that the art teaches and

Applicants specification acknowledges that antibodies to *S. aureus* Types 8 and 6 and 336 CPS induce type-specific opsonophagocytic killing by human PMNs *in vitro* and confer protection in animal infection models. What this study demonstrates is that vaccination-induced antibodies provide for a higher avidity antibody that provides for opsonization and protection in a relevant animal model challenge. Musher et al teach that the importance of the study is to underscore functional analysis of the vaccination-induced antibody and simply measuring antibody levels by ELISA. Additionally, it is noted that the specification has not measured functional activity as an index of protection, but merely antibody levels. Further, the art teaches "capsular polysaccharide conjugate vaccines have not been produced and proven to be safe and immunogenic in both healthy and in a significant percentage of immunocompromised patients. Antibodies generated in humans against these vaccines have been sown to mediate type specific oposonophogocytosis and to protect animals against lethal challenge with appropriate *S. aureus* isolates is specifically taught. Applicants are incorrect in asserting that the reference does not teach the conjugate vaccine. Applicants are directed to page 45, column 1, where the conjugates are specifically described. Further, Applicants admit that the clinical trial administered a formulation of type 5 and type 8 antigens each of which was conjugated to rEPA. As such, Applicants admit that the clinical trial practiced the claimed invention, that is administering the bivalent type 5 and type 8 conjugate vaccine and as such was also admittedly in "public use" more than one year prior to the filing of the claimed invention. Further, it appears that this was the same composition that was administered and declared in patients receiving hemodialysis to confer partial immunity against bacteremia (Shinefield et al, New England Journal of Medicine, 346(7):491-496, Feb 14, 2002; see page 491, column 1, "conclusions".). The UNX-1353 trial did not assess bacteremia as the endpoint. Applicants assert that the trial referenced in Fattom et al was a failure and that higher dosages were needed to provide for protection. This is not persuasive, Applicants are drawing conclusions from facts and evidence not presented to the examiner

and not attested to is not persuasive and not in the claims. It is also noted that the claims do not require any specific dosages.

Claims 1, 14, 15 and 17 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by Vaccine Weekly, September 30, 1996, p 10. for reasons made of record in the Office Action Mailed 4-7-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the vaccine is proprierity and there is no description of the components. This is not persuasive, Applicants had published the components of StaphVax in a previous document. The components of StaphVax were publically known in 1996, see Naso et al Advances in Experimental Medicine and Biology 397:133-40, 1996 which explicitly announces "The bivalent form of the capsular polysaccharides, which contains both the type 5 and type 8 polysaccharides conjugated to rEPA, is called StaphVAX. StaphVAX has been evaluated for safety and immunogenicity in over 80 volunteers including 40 healthy volunteers and 40 individuals with end-stage renal disease (ESRD)". As such, the inventors had announced the components of StaphVAX to the world by previous publication. Further it is noted that the Vaccine article does in fact indicate that it is a type 5 and type 8 conjugate vaccine. The claims only require conjugates. The skilled artisan would be readily apprised of the components. As such, one skilled in the art could practice the inveniton because it was fully enabled at the time of the invention. The inventors had disclosed the components of StaphVax in 1996. Applicants argue that there is no information regarding the protective efficacy of the StaphVAX. This is not persuasive as previously indicated, the administration of the same composition to the same patient population *in vivo* meets the limitation of the administration as set forth in the art and the administration inherently of the same composition inherently has the claimed functions. Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International

Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Claims 1, 14 and 15, 17-19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fattom et al, (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449) in view of Grabstein et al (U.S. Patent No. 5,747,024, issued May 5, 1998) is maintained for reasons made of record in the Office Action Mailed 4-7-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that since Fattom et al fails, so does the combination based on Fattom et al. The Fattom et al publication does not fail for reasons made of record supra and therefore the rejections based on Fattom et al are maintained. Applicants again argue protection. It is noted that the same composition is administered to the same population of patients and therefore would necessarily have the claimed activity. Fattom et al specifically teach "..we believe that S. aureus types 5 and 8 are not different from other encapsulated human pathogens where capsular polysaccharides were found to be useful as components of efficacious vaccines." (page 46, column 1).

Claims 1, 14, 15, 17 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fattom et al, (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449) in view of Fattom et al (Vaccine, 13(14):1288-1293, 1995) is maintained for reasons made of record in the Office Action Mailed 4-7-04.

Applicants' arguments have been carefully considered but are not persuasive. Applicants' argue that since Fattom et al fails, so does the combination based on Fattom et al. The Fattom et al publication does not fail for reasons made of record supra and therefore the rejections based on Fattom et al are maintained. Applicants again argue protection. It is noted that the same composition is administered to the same population of patients and therefore would necessarily have the claimed activity. Fattom et al

specifically teach "..we believe that S. aureus types 5 and 8 are not different from other encapsulated human pathogens where capsular polysaccharides were found to be useful as components of efficacious vaccines." (page 46, column 1).

New Rejections/Objections

Claims 1, 14, 15 and 17 are rejected under 35 USC 102(b) as being anticipated by Fattom et al Clinical Trial UNX-153, imitated in 1993.

Applicants admit on the record that the instantly claimed glycoconjugate type 5 and type 8 vaccine was administered to end-stage renal disease patients as set forth in Fattom et al (Annals of Medicine, 28:43-46, 1996, column 45, first full paragraph). 35 USC 102(b) provides for "in public use" in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 14, 15 and 17 are rejected under 35 USC 102(b) as being clearly anticipated by Fattom et al Clinical Trial performed between April 1998 and August 1999 in California on hemodialysis patients having end-stage renal disease in light of Shinefield et al (New England Journal of Medicine 346(7):491-496, Feb 14, 2002).

Shinefiled et al report the safety, immunogenicity and efficacy of a vaccine with *S. aureus* type 5 and Type 8 capsular polysaccharides conjugated to non-toxic recombinant Pseudomonas aeurgionosa exotoxin A, polysorbate 80 and sodium phosphate buffered saline performed in California between April 1998 and August 1999. 35 USC 102(b) provides for "in public use" in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 14, 15, 17 and 18 are rejected under 35 USC 102(b) as being anticipated by Naso et al (Advances in Experimental Medicine and Biology, 397:133-140, 1996).

Naso et al teach that the bivalent form of the capsular polysacchrides, which contains both type 5 and type 8 polysaccharides conjugated to rEPA, is called StaphVax. StaphVax has not been evaluated for safety and immunogenicity in over 80 volunteers including 40 healthy volunteers and 40 individuals with end-stage renal disease (ESRD) (page 136, second full paragraph). Naso et al teach that results in animals indicated that increased immune response to the vaccine can be achieved if the vaccine is formulated in adjuvants such as monophosphoryl Lipid A, Stimulon ™ and Novasomes™ and a non-phospholipid liposome -like delivery system and that human studies are to be initiated. As such, Naso et al teach the administration of the bivalent composition in saline or as combined with an adjuvant to boost the immune response. The administration of the same composition to the same patient population *in vivo* meets the limitation of the administration as set forth in the art and the administration inherently of the same composition inherently has the claimed functions. Ex parte Novitski 26 USPQ 1389 (BPAI 1993); Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999); Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999).

Claims 1, 14, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naso et al (Advances in Experimental Medicine and Biology, 397:133-140, 1996) in view of Fattom et al, (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449), Fattom et al (Vaccine, 13(14):1288-1293, 1995).

The teachings of Naso et al are set forth *supra*. Naso et al differs by not teaching immunization of other immune-compromised patient populations.

Fattom et al (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449), teach that type 8 CP-rEPA and/or type 5 CP-rEPA conjugate vaccines were initially evaluated in healthy human volunteers and that both conjugates elicit a 10-20 fold increase in CP-specific antibodies and sera tested provided for opsonophagocytic activity as compared to preimmune sera, and were able to protect animals against lethal challenge

with the appropriate *S. aureus* isolate. Fattom et al teach that the vaccine would be used to prevent staphylococcal infections by *S. aureus* in certain high-risk patient populations such as renal disease patients on dialysis, HIV patients, and individuals with scheduled high-risk surgery who are capable of mounting an immune response are likely to benefit from active immunization. Fattom et al teaches that they began the evaluation of active immunization studies in the target populations and demonstrated that 13 out of 16 hemodialysis patients responded with a 5-fold increase in titer when immunized with the type 5 CP-rEPA alone whereas 23 out of 23 healthy volunteers responded. Fattom et al teach that the data indicate that the conjugate vaccine is immunogenic and can be used for active immunization in some populations, other patient populations may require either higher doses of the vaccine or use of the vaccine with an adjuvant. Fattom et al teach that a clinical trial to evaluate the immune response and efficacy indications of the bivalent *S. aureus* vaccine in a larger population of end-stage renal disease patients on dialysis is underway (page 45, columns 1-2). Fattom et al teach that the results show that S. aureus types 5 and 8 are not different from other encapsulated human pathogens where capsular polysaccharides were found to be useful as components of efficacious vaccines (page 46, column 1, last paragraph).

Fattom et al (Vaccine, 13(14):1288-1293, 1995) teaches that adjuvants such as monophosphoryl lipid A, QS21 and Novasomes™ were able to increase the antibody levels five fold in a type 8 glycoconjugates as compared to the vaccine in the absence of the adjuvant.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to administer the bivalent *S. aureus* vaccine of Nago et al in combination with an immune adjuvant according to Fattom et al (Vaccine, 13(14):1288-1293, 1995) to renal disease patients of Nago et al or other immune compromised patients as directed by Fattom et al (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449) for protection from infection because Fattom et al (Annals of Medicine, 28:43-46,

1996; reference A3 on PTOL-1449) teach that the vaccine immunogenic in normal individuals, produces protective antibodies, that the results are not different from other encapsulated human pathogens where capsular polysaccharides were found to be useful as components of efficacious vaccines and Fattom et al (Vaccine, 13(14):1288-1293, 1995) teach that the use of adjuvants would provide for an expected five fold increased IgG response to a staphylococcal glycoconjugate vaccine antigen and Fattom et al (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449) teach that other patient populations may require higher dosages of the vaccine or use of an adjuvant to enhance the immune response.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Naso et al (Advances in Experimental Medicine and Biology, 397:133-140, 1996), Fattom et al, (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449), and Fattom et al (Vaccine, 13(14):1288-1293, 1995) as applied to claims 1, 14, 15, 17 and 18 above, and further in view of Grabstein et al (U.S. Patent No. 5,747,024, issued May 5, 1998).

The teachings of Naso et al (Advances in Experimental Medicine and Biology, 397:133-140, 1996), Fattom et al, (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449), and Fattom et al (Vaccine, 13(14):1288-1293, 1995) are set forth supra. The teachings as combined differ by not teaching β-glucan or granulocyte colony stimulating factor.

Grabstein et al teach cytokine-based immune enhancers/stimulants/adjuvants can be used to enhance a mammal's immune response to a vaccine antigen wherein the antigen is combined with IL-15 and G-CSF (see claim 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that the invention was made to substitute the adjuvants IL-15 or G-CSF of Grabstein et al for the adjuvants in the method of Naso et al (Advances in Experimental Medicine and Biology, 397:133-140, 1996), Fattom et al, (Annals of Medicine, 28:43-46, 1996;

reference A3 on PTOL-1449), and Fattom et al (Vaccine, 13(14):1288-1293, 1995) as combined supra because Nago et al teaches that the vaccine is immunogenic in ESRD patients, Fattom et al (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449) teach that the vaccine is immunogenic in normal individuals and that antibodies protect against lethal challenge and Grabstein et al teach that the use of adjuvants would provide for an increased immune response to a vaccine antigen and Fattom et al (Annals of Medicine, 28:43-46, 1996; reference A3 on PTOL-1449) teach that other patient populations may require higher dosages of the vaccine or use of an adjuvant to enhance the immune response.

37 CFR 1.105 REQUEST FOR INFORMATION

An issue of public use or on sale activity has been raised in this application. In order for the examiner to properly consider patentability of the claimed invention under 35 U.S.C. 102(b), additional information regarding this issue is required as follows: any information regarding Identification of any use of the claimed invention known to any of the inventors at the time the application was filed notwithstanding the date of the use and any description of such use in any publication. Applicant is reminded that failure to fully reply to this requirement for information will result in a holding of abandonment.

Citation of Relevant Prior Art

Robbins et al, (Journal of Infectious Diseases 161(5):821-832, 1990). Robbins et al teach protective conjugate vaccines of the art may confer protective immunity to patients with partial immunodeficiencies not covered by capsular polysaccharides of *Haemophilus influenzae* type b alone (pages 823-824). Robbins et al teach conjugate vaccines for active and passive immunization against Bacteremia caused by *Staphylococcus aureus* and antibodies elicited by conjugates facilitated opsonizaton of *S. aureus* by human PMNL, a biologic correlate of protective immunity see pages 827-828.

Sood et al (Drug Discovery Today, 1(9) :381-387, 1996). Sood et al is cited to teach that the conjugation of polysaccharides to carrier proteins generally enhances polysaccharide immunogenicity and renders the immune response T cell dependent. Such enhancement of immunogenicity has made the use of conjugate vaccines possible in populations that are otherwise unresponsive to polysaccharide vaccines. The authors discuss the value of capsular polysaccharide vaccines and their ability to elicit protective immunity against infectious bacteria.

Shinefield et al (J Pediatr Infect Dis, 19(4):394-397, 2000). Schinefield et al teach that pneumococcal conjugate vaccines are immunogenic after primary and booster vaccination in young children and in children and adults with immunodeficiencies. Shinefiled et al teach that evidence indicates that the pneumococcal conjugate vaccines are effective in reducing invasive pneumococcal disease as well as acute otitis media and pneumonia in children.

Fattom et al (Advances in Renal Replacement Therapy, 3(4):302-308, 1996). Fattom et al teach that hemodialysis patients responded with IgG1 and IgG2 subclasses, that were biologically active in the in vitro opsonophagocytosis assay when immunized with the bivalent, type 5 and type 8 conjugate vaccines. Strategies for improving the responsiveness of dialysis patients being discussed or evaluated are: (1) dosing studies to determine the dose needed to elicit higher levels of CP antibodies, (2) the use of adjuvants or delivery systems to increase the immunogenicity of vaccines, and (3) boosting of the immune response by re-immunizing patients when titers fall to low levels. Studies have shown that re-immunization of renal patients resulted in restoration of specific IgG levels to near previous maximal values. Studies in animal also show that adjuvants to be effective in increasing antibody levels in response to vaccination with these vaccines.

Campbell et al (Clinical Infectious Diseases, 23(1):179-181, 1996) teaches that preliminary results indicate that active immunization of potential pathogens is possible in victims of acute trauma using conjugate vaccines.

O'Brien et al (Pediatrics, 106(5):965-972, Nov 2000) teaches that the heptavalent pneumococcal vaccine conjugated to CRM197 provided for dramatic increase in the antibody concentration in infants with sickle cell disease and that the concentrations were in the same range as those without sickle cell disease and in the same range of antibody levels in infants without sickle cell disease in a study that demonstrated vaccine efficacy.

Ambrosino et al (Journal of Pediatric Surgery, 27(8):1045-1048, 1992 teaches that the new Haemophilus influenzae type b conjugate vaccine was able to induce high levels of protective antibody when immunized before splenectomy.

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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